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PATENT
Attorney Docket No. **HOGAN-04448**
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :	Kirk Hogan	
Serial No.:	09/613,887	Group No.: 1655
Filed:	07/11/01	Examiner: J.E. Goldberg
Entitled:	Methods and Compositions for Perioperative Genomic Profiling	

AMENDMENT AND RESPONSE TO OFFICE ACTION DATED SEPTEMBER 22, 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: 3-22-01 By: Mary Ellen Waite
Mary Ellen Waite

Sir/Madam:

The following communication is responsive to the Office action mailed September 22, 2000, due on or before December 22, 2000. A petition for a three month extension of time from December 22, 2000 to March 22, 2001 is submitted. The Applicant respectfully requests reconsideration of the Application in view of the following amendment and remarks.

I. IN THE CLAIMS:

Please substitute the following Claims for their corresponding pending claims:

1. (Amended) A method for generating a genomic profile comprising:

a) providing a sample from a perioperative subject, and

b) subjecting said sample to an assay for detecting two or more genetic markers to generate a genomic profile for use in selecting a perioperative course of action.

13. (Amended) A method for generating a genomic profile comprising:

a) providing a sample from a perioperative subject; and

b) subjecting said sample to an assay for detecting two or more genetic markers to generate a genomic profile for use in selecting a surgical procedure treatment course of action.

17. (Amended) A method for generating a genomic profile comprising:

a) providing a sample from a perioperative subject; and

b) subjecting said sample to an assay for detecting two or more genetic markers associated with a pharmacological response to generate a genomic profile for use in selecting a surgical procedure treatment course of action; and

c) subjecting said subject to a surgical procedure, wherein the conditions for said procedure are based on said genomic profile.

II. IN THE SPECIFICATION: OBJECTIONS

Please substitute the following paragraph for the paragraph beginning on page 24, line 11.

As used herein, the terms "SNP," "SNPs" or "single nucleotide polymorphisms" refer to single base changes at a specific location in an organism's (*e.g.*, a human) genome. "SNPs"

can be located in a portion of a genome that does not code for a gene. Alternatively, a "SNP" may be located in the coding region of a gene. In this case, the "SNP" may alter the structure and function of the protein in which it is located. In some instances, a "SNP" may affect an individuals response to a medical procedure or surgery (*e.g.*, response to an anesthetic or pain medication). The location and sequences of many "SNPs" are available in public databases (*See e.g.*, NCBI's dbSNP available at the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health web site) as well as private databases.

Please substitute the following paragraph for the paragraph beginning on page 26, line 21 (*i.e.*, the last paragraph on page 26 that spans pages 26 and 27).

In addition to known SNPs, a variety of nucleotide sequence information describing wild type and mutant alleles of a large number of genes is available in public databases including, but not limited to DbEST (available at the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health web site); EBI/EMBL (available at the EMBL European Bioinformatics Institute public web site); EBI (available at the EMBL European Bioinformatics Institute public web site); EMBL (available at the EMBL European Bioinformatics Institute public web site); The Genome Database (GDB) (available at Genome Database public web site); GeneCards (Rebhan *et al.*, GeneCards: encyclopedia for genes, proteins and diseases. Weizmann Institute of Science, Bioinformatics Unit and Genome Center, Rehovot, Israel, 1997); GeneClinics (GeneClinics: Clinical Genetic Information Resource [database online], Copyright, University of Washington, Seattle. 1995-, Updated weekly); Genethon (available from Human Genome Research Centre public web site); GSDB (available from the National Center for Genome Research public web site); HGP (available from the Human Genome Project public web site); Human Gene Mutation Database (available at the Human Gene Mutation Database public web site); NCBI (available at the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health web site); OMIM (available at the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health web site); PubMed (available at the National Center for Biotechnology Information, National

Library of Medicine, National Institutes of Health web site); Research Tools (NCBI) (available at the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health web site); RHdb (available at the EMBL European Bioinformatics Institute public site); Stanford Human Genome Center (available at the Stanford Human Genome Center public web site); HUGO (available at the The Human Genome Organization public web site); TIGR (available at the Institute for Genomic Research public web site); The National Human Genome Research Institute (available at the National Human Genome Research Institute public web site); The Whitehead Institute Center for Genome (available at the Whitehead Institute for Biomedical Research/MIT Center for Genome Research); Unigene (available at the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health web site); University of Oklahoma (available at the University of Oklahoma's Advanced Center for Genome Technology public web site); and WEHI (available at the Walter and Eliza Hall Institute of Medical Research public web site). One skilled in the relevant art understands that nucleotide sequence data may be also be obtained from additional sources, including, but not limited to public and private databases; as well as experimentally.

REMARKS

A version of the amended claims with markings is attached hereto at Tab 1. A version of the amended specification with markings is attached hereto at Tab 2. A copy of the pending Claims is attached to this communication at Tab 3 for the Examiner's convenience.

In the Office Action dated September 22, 2000, the Examiner objected to an embedded hyperlink and/or other form of browser-executable code. The PTO objects to the use of hyperlinks because hyperlinks create a live web link in published patents, which may link to commercial web sites, violating a PTO policy forbidding linking to commercial sites. Each of the hyperlinks in the present Specification is a link to public non-commercial web sites making this concern moot. However, Applicant has deleted the executable code and replaced it with the corresponding identity of the web site provider. For this reason the Applicant respectfully requests that this objection be withdrawn.

In the Office Action dated September 22, 2000, the Examiner also made a number of arguments pertaining to written description, non-enablement, indefiniteness and prior art

rejections. To minimize redundancy before responding to each rejection in turn, the following description of the presently claimed invention is provided to aid the Examiner in reviewing the application. The Applicant provides descriptions of various elements of the present invention to help familiarize the Examiner with aspects of the invention. These descriptions are provided simply to further an understanding of the invention and are not meant to limit the scope of the claims. Indeed, in describing certain aspects of the presently claimed invention it is helpful to describe embodiments that may be of narrower scope than those encompassed by the claims.

Patients undergoing surgery and anesthesia exhibit wide variation in their physiologic and pathologic responses to drugs and trauma, such that an intervention that would be perfectly safe in one individual carries the potential for grievous harm and even death to another. A substantial proportion of inter-individual variation is genetic, but prior to the present invention, this risk was unaccounted for. Were genetic risk to be known in advance of surgery and anesthesia, selection of alternative interventions would be life-saving. The present invention solves this problem by providing caregivers a profile of genetic susceptibilities upon which therapeutic management can be tailored.

In some embodiments of the invention, a single patient's sample is simultaneously assayed for multiple alleles of interest to generate a genomic profile. Each allele constituting the profile falls within one of the categories described in Section I. C. of the Specification "Categories of Markers" (page 29) i.e. alleles causing abnormal pharmacokinetic responses, alleles causing unsuspected co-existing diseases, etc. To be included, each allele should also fulfill explicit criteria of analytical validity (the allele is reliably detected), clinical validity (the allele accurately predicts the phenotype), and clinical utility (the allele specifies an available step to improve patient safety), described in Section I. B. "Criteria for Selection of Markers" (page 27). Selection of markers falling within these categories and meeting these inclusion criteria, provides the genus of markers, allowing sequence information from any source to be properly assembled into the invention.

It is not required that caregivers must know the method of profile construction or data acquisition, but by virtue of the clinical utility requirement in the inclusion criteria, caregivers will know what to do with the results, or presence of an allele in question is not sought. So, for example, the presence of a marker predicting a toxic response to a drug (e.g., malignant hyperthermia) will permit the caregiver to select a safer alternative agent or anesthetic regimen

(e.g., a regional anesthetic), or the presence of a marker associated with a complicating condition (e.g., thrombosis) will permit heightened monitoring and prophylaxis.

The present invention is not a method for identifying new DNA sequences, but rather incorporates known sequence information selected from any suitable sources (e.g., presented in the Specification I.A; "Sequence Data" (page 26), by categorical criteria described in the Specification I.B. and I.C). Other than meeting the categorical criteria as described, no common structural feature for the markers selected is required. Practice of the invention is not contingent on a complete set of all relevant makers, nor must the results from all markers tested be abnormal for each particular patient. Because genomic information is not currently profiled in the perioperative interval by any method, many, several, one or no abnormal markers in a given profile tested for a specific patient may be equivalently informative in assessing risk i.e. all genomic data, whether normal or abnormal, will assist the caregiver in selecting the safest possible course. By surmounting constraints of cost, speed and accuracy, profiles permit alleles acting synergistically to be singly and simultaneously evaluated. However, the genomic profiles generated under the methods of the present invention do not dictate a fixed anesthetic or surgical course to the exclusion of other variables and factors falling with the ambit of the caregiver's judgment. Perioperative genomic profiles of the present invention illuminate a large source of patient-to-patient variation that is presently concealed, but the results obtained are to be weighed in the full context of a patient's overall medical and surgical status.

III. REJECTIONS

For clarity, the rejections at issue are set forth by number in the order they are herein addressed.

A.) WRITTEN DESCRIPTION

1.) Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was

filed, had possession of the claimed invention. Specifically, the Examiner argues that the presently claimed invention is not properly described because:

a) There is not an adequate description of the genus of genetic markers used
b) The markers lack a common structural feature
c) Knowledge in the art does not readily identify the incorporated markers
d) The examples given do not support the genus

The Applicant must respectfully disagree and address each point in turn.

2.) The Examiner's various arguments under U.S.C. 112 are bound by review as if the invention claimed was a composition of matter, and it is not. The invention does not claim discovery of newly identified DNA sequences, nor is it dependent on knowledge of a finite number of specific sequences. Newly identified sequences meeting categorical criteria under Specification Sections I.B. and I.C. are incorporated. By analogy, claims to a method of databasing and displaying sequence information are properly described without describing every (or any) sequence that may be used in the method. A description that explains how to identify and process the genus of markers, sample and data acquisition, data archiving and dissemination to caregivers is similarly proper, without disclosure of specific sequence information of each and every (or any) marker that may be used in the method.

3.) Conversely, with respect to the review of the invention's methods claims, the Examiner's arguments above are not relevant.

a) There is adequate description of the genus of markers

The Examiner argues that "There is not adequate description of the genus of genetic markers which may be used to screen for a patient's response to anesthesia and related medication." (Office Action, page 3). To the contrary, Sections I.B. "Criteria for Selection of Markers" (page 27) and I.C. "Categories of Markers" (page 29) of the Specification specifically and unambiguously teach the genus of the markers. Markers falling within these

categorical criteria are incorporated. Markers falling without are not. The line dividing the two is bright, and its plain language description within the Specification is presented in detail.

b) A common structural feature is not claimed

The Examiner argues that "The specification has also not identified a structural feature of the genetic markers which may be used to screen for a patient's response to anesthesia and related medications which would be common to all members of the genus that constitutes a substantial portion of the genus." (Office Action, page 3). No common structural feature of incorporated genetic markers is identified because none is claimed. Nor is a structural feature common to the incorporated genetic markers a requirement for the invention to be practiced as claimed. To the contrary, an important advantage of the invention is the capacity to simultaneously detect alleles of life-saving significance despite widely divergent structural features e.g.. sequence identity, single base pair substitutions, insertions, deletions, splice variants as detailed in Section I.A. "Sequence Data" of the Specification (page 26). Applicant is not claiming a composition where, for example, one might be required to provide a common structural feature to define the claimed genus structure. Instead, Applicant claims a method that employs any number of genetic markers, the selection of which is described in more than sufficient detail in Specification as discussed above.

c) The Specification identifies the incorporated markers

The Examiner argues "The general knowledge in the art concerning genetic markers which may be used to screen for a patient's response to anesthesia and related medication does not provide any indication of how to readily identify these genetic markers." (Office Action, page 3). In addressing this point the Examiner has merely restated one facet of the problem solved by the present invention. It is true the general knowledge in the art concerning genetic markers does not teach how they should be identified for perioperative use. But, that which the general knowledge of genetic markers does not and cannot provide, is in fact taught by the present invention as claimed and specified at I.B. and I.C.

d) The examples given do support the genus

The examiner argues that the invention "teaches only a handful of mutations with ten different genes which have been identified as having any effect on the response to anesthesia." (Office Action, page 2). The Examiner's statement is incorrect. The representative mutations referred to are clearly presented within the Specification as an "Example" and labeled as such at page 46. Moreover, under "Experimental" the Specification clearly states: The following *example* is provided in order to demonstrate and further illustrate certain preferred embodiments and aspects of the present invention and *is not to be construed as limiting the scope thereof.* (emphasis added, page 45).

The Examiner also argues at several junctures that "The twenty mutations described are not representative of the genus of genetic markers which may be used to screen for a patient's response to anesthesia and related medication." (Office Action, page 3) and ". . . the description of only twenty members of this genus is not representative of the variants of the genus and is insufficient to support the claims." (Office Action, page 3). To the contrary, the 20 representative mutations in the Example provided and so labeled are exactly on point with the Criteria and Categories for Selection of Markers in Sections I.B. and I.C. of the Specification. In aggregate, and as explicitly presented, the markers of the example teach a broad variety of sequence alterations (coding and non-coding SNPs, insertions, deletions, splice variants), selection criteria (analytical validity, clinical validity, clinical utility for each allele), and categories (pharmacokinetic alleles, pharmacodyamic alleles, co-existing disease alleles). In addition, and also contrary to the Examiner's assertions, many other representative alleles in addition to those of the example are presented in Section I.D. of the Specification (pages 31-34). Thus, the Examiner has erroneously correlated the scope of the examples given with the scope of the genus of markers claimed and explicitly specified.

4.) The Applicant believes that the Specification provides ample and proper written description for the claimed invention. Explicit criteria denominating a detailed and functional genus of genetic markers are provided. No common structural feature of the genetic markers is claimed or necessarily desired for successful practice of the invention. The examples presented of constituent alleles and profiles represent a diverse and informative range of genetic markers, and the claims and Specification of the invention together with knowledge in

the art, denote additional examples of known sequences for incorporation. Conversely, the Examiner offers no authority, reference or personal experience in support of any item of the declared rejections. The Applicant believes that the Specification adequately provides a written description for genetic markers which may be used to screen for a patient's response to, for example, anesthesia and surgery, and that the foregoing arguments traverse the 35 U.S.C. 112 rejection. For the reasons provided above, Applicant respectfully requests that the rejection be withdrawn.

B.) ENABLEMENT

1.) Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because allegedly "The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." Specifically, the Examiner argues that the presently claimed invention is not enabled because:

a) The invention does not reasonably provide enablement for detecting **any** two genetic markers

b) The invention does not reasonably provide enablement for generating a profile for use in selecting **any** operative course of action

c) The Specification teaches only twenty mutations in ten genes

d) The clinical validity and clinical utility of the twenty mutations in 10 genes is challenged

e) The skilled artisan would require undue experimentation to evaluate which mutations are associated with anesthesia and medical complications

f) The Specification does not teach what an appropriate operative course of action entails

g) The Specification does not teach any specific combination of markers, or to determine appropriate courses of action for all the various combinations if detected

h) The Specification does not provide guidance as to how to select the specific anesthesia based solely upon these markers

i) The Specification does not provide any distinction between different types of anesthesia and their association with different mutations

j) It is unpredictable for the skilled artisan to determine which of the provided mutations would have complications with specific anesthetics

k) The detection of two genetic markers would not necessarily provide enough information to select an operative course of action appropriate for a particular patient

The Applicant must respectfully disagree and address each point in turn.

a) The invention provides enablement for detecting <u>any</u> two genetic markers

The Examiner argues that ". . . the specification, while being enabling for a method for detecting Butyrylcholinesterase deficiency, poor debrisoquine metabolism, thrombus, and malignant hyperthermia based upon the detection of two or more genetic markers for use in generating a genomic profile which is used in selecting an operative course of action, does not reasonably provide enablement for detecting **<u>any</u>** two genetic markers . . ." (Office Action, page 4). To the contrary, the Specification explicitly and in detail provides enablement for detecting <u>any</u> two genetic markers under section II. "Assays for Generating Genomic Profiles" (pages 34-45). The Examiner offers no authority, reference or personal experience to challenge the analytical validity of the assays as embodied.

b) The invention provides enablement for generating a profile for use in selecting <u>a perioperative</u> course of action

The Examiner argues that the Specification ". . . does not reasonably provide enablement for . . . generating a profile of use in selecting **<u>any</u>** operative course of action." (Office Action, page 4). The Examiner appears to have misread the claims. Specifically Claim 1.b. states "for use in selecting **<u>an</u>** operative course of action" (amended in this Response to "**<u>a</u>** perioperative course of action"), not **<u>any</u>** operative course, and Claims 13.b. and 17.b. "for use in selecting **<u>a</u>** surgical treatment course of action", not "**<u>any</u>** surgical treatment course of action." Alternative perioperative courses (i.e. clinical utility) are an intrinsic criteria of alleles selected for inclusion in the profile. Because the invention does not

claim to select any perioperative course of action, but simply those indicated by the presence or absence of tested alleles in view of other facts known to the treating physician, the Applicant believes it is fully enabled as presented in the Specification.

c) The Specification teaches a genus of mutations of relevance in the perioperative interval

The Examiner argues at multiple points within the non-enablement rejection that only those genes and mutations presented for the purpose of an example represent the scope of the invention: "The specification teaches ten distinct genes . . " (Office Action, page 4), "The specification teaches mutations in the ten identified genes . . ." (Office Action, page 5), "First, the specification only provides twenty mutations which have association with "selection of an operative course of action." (Office Action, page 8), "Secondly, the specification only contemplates butyrylcholinesterase deficiency, poor debrisoquine metabolism, thrombus and malignant hyperthermia (pg. 48-49)." (Office Action, page 8). These statements are in error. As the Applicant has argued in responses 3.a. and 3.d. to the Written Description rejection (see above), the application more than sufficiently teaches selection procedures for a discrete and finite genus of markers that meet the appropriate criteria under Sections I.B. and I.C. of the Specification and is not confined to the scope of the examples provided. While the examples given fully support this genus, they are clearly labeled to be construed as examples only (see above), and thereby do not limit the scope of the invention to those examples presented. The Examiner has not presented any basis why one skilled in the art would not be able to follow the instructions in the present invention (*e.g.*, the instructions spelled out in Sections I.B. and I.C. of the Specification) in using the methods of the presently claimed invention. The knowledge of every marker sequence and mutation is not needed to practice the present invention (i.e., the presently claimed invention is not a method for identifying genetic markers).

d) The clinical validity and clinical utility of the mutations presented as examples are well-established

On pages 5 through 8 of the Office Action the Examiner challenges the clinical validity and clinical utility of each of the alleles as taught in references presented by the

Applicant as examples. These rejections are not relevant to a non-enablement rejection for the reasons stated above. However, Applicant notes that with respect to specific anesthesia applications, the references cited by the Examiner highlight the usefulness of the present invention and do not provide support for the Examiner's non-enablement rejection. For example, the Examiner quotes Hogan (1998) stating that "until very nearly all mutations in all predisposing genes are charted, the causality for each is unambiguous, offering family genotyping for purpose other than research will be premature." (page 474, col 1), and Brandt et al (1999) stating "interpretation must be performed with care because lack of the particular mutation segregating in the family does not exclude absence of further independent known mutations." These statements, while correct, are irrelevant to the present invention since family screening is not claimed or specified, nor is family screening the problem which the present invention solves i.e. family screening is very different from perioperative screening of individual patients.

Other references cited by the Examiner challenge the clinical validity of the chosen examples because of genetic heterogeneity underlying a trait (e.g. Sudbrak et al. (1993), O'Brien et al. (1996)). Not only does the claimed invention function under genetic heterogeneity, but it embodies the only methods for doing so i.e. profiling resolves genetic heterogeneity by simultaneous assays of multiple genotypes. Still other clinical validity and clinical utility challenges based on references cited by the Examiner are artifacts due to the identification of a few specific references that do not provide an understanding of the art as a whole. For example, the Examiner cites Tsai et al (1996) which ". . .teaches that an insertion in the CBS gene seems to affect the activity of the CBS enzyme, the prevalence is somewhat increased in patient with premature coronary-heart disease, although not statistically significant." (Office Action, page 5) However, this citation was provided by the Applicant in the Table 3. of examples within the Specification to document allele recognition, characterization, and incidence. The statistically significant relevance of CBS markers to vascular disease (i.e. clinical validity) appears in Kruger WD et al. Polymorphisms in the CBS gene associated with risk of coronary artery disease and increased responsiveness to total homocysteine lowering by folic acid. *Molecular Genetics and Metabolism* 70:53-60, 2000.

Finally, others of the Examiner's comments are in clear error. For example, the

Examiner states in reference to the manuscript by Korte et al. (1998) "As seen in Table 2 and 3, the results of the detection assay for the two genetic markers were observed." (Office Action, page 6). To the contrary, the "molecular markers" in the Korte reference are thrombin generation prothrombin fragment F1+2 and fibrin degradation (D-dimer) markers. These are proteins, not genetic markers.

e) The skilled artisan requires no undue experimentation to evaluate which mutations are associated with anesthesia and medical complications

The Examiner argues that "Based upon the teachings in the Specification and the art, the skilled artisan would be unable to practice the invention as broadly as claimed." (Office Action, page 8), and "It would be undue experimentation for the skilled artisan to study the voluminous known mutations and determine association with anesthesia and medical complications." (Office Action, page 8). To the contrary, Sections I.B. and I.C. of the Specification instruct precisely how the genus of relevant markers is identified. Since only mutations meeting explicit categorical criteria are included in the profile, no experimentation whatsoever is required of the skilled artisan. If the skilled artisan is an anesthesiologist then that person would know what to do and not to do for a patient with mutations in any of the alleles presented in the example, those specified more broadly as examples on pages 31-34 of the Specification, or more broadly still those extracted from the specified databases on page 26 meeting I.B. and I.C. categorical criteria. If the skilled artisan were a molecular biologist or geneticist, Sections I.B. and I.C. recite precisely which mutations are of relevance with no experimentation required. Because the invention is not a method or composition claiming new gene discovery, and because only those alleles of established validity and utility are incorporated in the specified embodiments, the skilled artisan is not encumbered by any undue experimentation whatsoever. Alleles failing to meet the inclusion criteria as specified by the present invention will not be tested. For those that are tested, the skilled artisan will know what operative course of action to take or how to evaluate the information provided by the assay in deciding among options.

f) The Specification teaches what an appropriate operative course of action entails

The Examiner argues that "The specification does not teach any specific combination of markers and what the appropriate 'operative course of action' entails" (Office Action, page 8). To the contrary, the Specification teaches combinations of markers meeting categorical criteria of Sections I.B. and I.C.

Examples of detailed, specific and life-saving operative courses of action indicated by genomic data are presented on pages 30-34 of the Specification at Section I.D. "Applications and Interventions of Specific Markers."

Since only mutations meeting explicit categorical criteria are included in the profile (e.g., markers are selected that have clinical utility), no experimentation whatsoever is required of the skilled artisan. A treating physician would know what to do and not to do for a patient with mutations in the alleles. As discussed above, the genomic profiles generated under the methods of the present invention do not dictate a fixed course of action to the exclusion of other variables and factors falling with the ambit of the caregiver's judgement. Perioperative genomic profiles of the present invention illuminate a large source of patient-to-patient variation that is presently concealed, but the results obtained are to be weighed in the full context of a patient's overall medical and surgical status.

g) The invention does not claim to teach appropriate courses of action for all the various combinations if detected

The Examiner argues that "It would require undue experimentation for the skilled artisan to minimally take the 20 mutations provided in the Specification and determine appropriate courses of action for all the various combinations if detected. Such combinations would include all of the different pairs of mutations, all of the different triples of the mutations and so forth." (Office Action, page 8). The Examiner has misconstrued the claims of the invention. No claim is made that each combination or permutation of alleles will have a distinct course of action. The treating physician makes a decision based on the results of the assay. This decision may be based on the results for a single marker or multiple markers even though many more markers are tested. As embodied, alleles are assayed simultaneously and in profile to take advantage of cost, efficiency and accuracy attributes of the incorporated

genotyping technologies. Not only does the invention teach the skilled artisan exactly which genetic markers comprise the correct genus without undue experimentation (i.e. those meeting Section I.B. and I.C. categorical criteria of the Specification), but an appropriate course of action (i.e. clinical utility) is itself one of these criteria.

h) The invention does not claim to provide guidance as to how to select the specific anesthesia based solely upon these markers

The Examiner argues "Furthermore, the specification does not provide any guidance as to how to select the specific anesthesia based solely upon these markers and their correlation to an invasive vs. non-invasive procedure." (Office Action, page 8). The Examiner has misconstrued the claims of the invention. At no point in the application is it claimed or specified that an anesthetic, surgical or medical course of action will be based solely "on these markers." Implications of the presence or absence of mutations in the perioperative genomic profile are appraised by the skilled artisan/caregiver in the context of a specific patient taking into account other diagnoses, medications, life experiences and exposures. The invention makes no such claim to contravene the edicts of good medical practice in the manner suggested by the Examiner.

An example of genomic marker's contribution to the clinical decision between invasive and non-invasive procedures is presented on page 33, second paragraph of the Specification under section I.D. "Applications and Interventions of Specific Markers."

i) The Specification does distinguish between different types of anesthesia and their association with different mutations

The Examiner argues "The specification does not appear to provide any distinction between different types of anesthesia and their association with different mutations." (Office Action, page 9). The Examiner has misconstrued the claims. The invention does not claim that specific mutations are useful in general anesthesia while others are useful in regional anesthesia. Rather the invention involves mutations fulfilling categorical criteria I.B. and I.C. of the Specification that are helpful in determining whether regional or general anesthesia is safer and to be preferred for a specific, individual patient. The patient will be tested for alleles of relevance. The resulting profile will indicate which course of action, regional or general

anesthesia, is most appropriate and how to conduct the anesthetic with the greatest safety i.e. dose, regimen, route of administration given the patient's genetic constitution. The same logic applies to the distinction between invasive and non-invasive surgery. Tested alleles contribute to the selection of the most appropriate management for patients who are tested for a full profile of alleles.

Many examples of associations between different types of anesthesia and association with different mutations are presented in Tables 1.- 4., and pages 31-34 of the Specification.

j) It is entirely predictable for the skilled artisan to determine which of the provided mutations would have complications with specific anesthetics

The Examiner argues "It is unpredictable for the skilled artisan to determine which of the provided mutations would have complications with specific anesthetics." (Office Action, page 9). Arguments put forward by the Examiner that the invention does not provide enablement for determining which of the provided mutations would have complications with specific anesthetics are unsupported by cited authority, reference or personal experience (i.e., they are improper conclusory statements). To the extent the Examiner is relying on referenced material or personal knowledge, Applicant requests that the reference(s) and/or Examiner's factual affidavit be provided. In contrast to the Examiner's argument, if it were unpredictable, the allele would not be included on the profile. To be considered for inclusion, every mutation should have predictable consequences i.e. clinical validity (Section I.C.). The skilled artisan therefore knows what complications are predictable, and which interventions to select by virtue of the tested mutations. A detailed list of examples directly tying mutations to complications arising from the use of specific anesthetics is included in the Specification at pages 31-34 and Tables 1.- 4.

k) The detection of two genetic markers provides enough information to select an operative course of action appropriate for a particular patient

The Examiner argues "Thirdly, based upon the teachings in the art, the detection of two genetic markers would not necessarily provide enough information to select an operative course of action appropriate for a particular patient." The Examiner's statement is not relevant to the claims of the invention. The invention as specified does not claim to remove all

responsibility from a caregiver in selecting an appropriate course of action. Two or more genetic markers may or may not determine a perioperative course depending on what the markers are and whether they are present or absent in a given patient. Not testing fails to give the patient the chance to avoid loss of life or limb from an undisclosed genetically predisposing condition. Because a specific allele will determine a course of action in some patients and not in others, it is relevant to perform the analysis in profile for many alleles simultaneously, particularly when traits are associated with genetic heterogeneity.

The Examiner concludes the non-enablement rejection with the statement "Therefore it would be undue experimentation for the skilled artisan to detect any genetic markers and infer an association between the markers and response to anesthesia based solely upon guidance provided in the specification which teaches twenty mutations." (Office Action, page 10). To the contrary, the Specification provides full enablement for the invention as claimed. As Applicant argues above, no experimentation whatsoever is required of the skilled artisan to select and use the constituent alleles of the perioperative genomic panel. The skilled artisan is under no burden to "detect" genetic markers or to "infer" an association between the markers and response to anesthesia, since these are established as criteria prior to inclusion within the profile. Guidance provided in the Specification exactly teaches the full and finite genus of relevant genomic markers, and is not confined, as the Examiner has argued, to the examples presented in the Specification. Details of the Specification, together with the examples provided, fully enable selection of alternative safer anesthetic and surgical management based on the results of perioperative profiles. Arguments put forward by the Examiner that the invention does not provide enablement for generating profiles of use in selecting a perioperative course of action are unsupported by cited authority, reference or personal experience. The Examiner has provided no basis for suggesting that a skilled artisan would be unable to apply the categorical criteria presented in Sections I.B. and I.C., or that the skilled artisan would be unable to interpret the results of perioperative genomic profiles in such a fashion so as to significantly improve the safety of patients undergoing surgery and anesthesia. The Applicant believes that the Specification adequately enables the invention as claimed, and that the foregoing arguments traverse the 35 U.S.C. 112 non-enablement

rejection. For the reasons provided above, Applicant respectfully requests that the rejection be withdrawn.

C. THE CLAIMS ARE DEFINITE

The Examiner has rejected Claims 1-20 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, for the following arguments:

a) The Examiner argues that " . . . claims 1,13, and 17 lack a preamble which sets out the intent of the claims. Thus the preamble does not meet the final process step." (Office Action, page 11). Applicant respectfully disagrees and asserts that the claims are definite. However, in order to further Applicant's business interests and the prosecution of the present invention, while not acquiescing to the Examiner's arguments, language is added to the preambles of Claims 1, 13 and 17 as follows:

Claim 1 - "A method for generating a genomic profile comprising:"

Claim 13 - "A method for generating a genomic profile comprising:"

Claim 17 - "A method for conducting a surgical procedure comprising:"

Applicant reserves the right to prosecute the original claims (or similar claims) in the future.

b) The Examiner argues that "Claims 1-20 are indefinite over the recitation providing "an assay" because it is unclear how an assay may be provided. One may clearly imagine the reagents necessary for a set assay be provided, but for one to provide an assay is unclear." (Office Action, page 11). To the contrary, Section II "Assays for Generating Genomic Profiles" of the Specification, pages 34 - 42, recites multiple methodologies that clearly meet the requirement for provision of methods for an assay. However, in order to further Applicant's business interests and the prosecution of the present invention, while not acquiescing to the Examiner's arguments, Applicant has amended the claims to remove the phrase "providing an assay." Applicant reserves the right to prosecute the original claims (or similar claims) in the future.

c) The Examiner argues "Claims 1-20 are indefinite over the recitation "for use in selecting an operative course of action" because it is unclear whether generating a genomic profile meets the limitations of the claims or whether the claim limitations require the genomic profile is in fact used in selecting an operative course of action. (Office Action, page 11). To the contrary, Claims 1-20 require that the genomic profile be generated, and that the genomic profile is defined functionally in the claim as one that is configured for use in selecting an operative course of action. Specific examples reciting use of genomic data for selection between alternative anesthetic and surgical interventions are presented in the Specification at I.D. "Applications and Interventions of Specific Markers" (pages 30-34) and within Tables 1. - 4. An explicit refutation of the Examiner's argument is made in the Specification I.B. "Criteria for Selection of Markers", page 28 paragraph 3: "In particularly preferred embodiments, markers are selected that provide information that can be used to alter the course of treatment (i.e. the markers have clinical utility)." The method does not require that the genomic data actually be used - the skilled artisan/caregiver may be aware of another over-riding non-genomic, patient-specific variable. Finally, the Specification makes clear that normal as well as abnormal genomic results are encompassed: "In addition, markers are selected for which a negative result (e.g. the absence of an underlying condition) has clinical utility (e.g. aids in the differential diagnosis of a disease)."

d) The Examiner argues " Furthermore it is unclear what an operative course of action includes. It is unclear whether an operative course of action may essentially be any course of action which is operative, i.e. which works." (Office Action, page 11). While Applicant believes the claims are definite, to highlight the distinction between a <u>perioperative</u> course of action, and an <u>operative</u> course of action, Claim 1 has been amended to use the former language. It is noted that a definition of operative as "Of, pertaining to, or resulting from a surgical operation" (Random House Dictionary, 2nd Edition, 1985, page 871) also fulfills the intended meaning.

e) The Examiner argues that "Claims 1-20 are indefinite over the recitation "two or more genetic markers" because it is unclear whether detection of a gene constitutes a genetic marker, detection of a chromosome is genetic marker, absence of detecting a

chromosomal region is a genetic marker or whether a mutation within a gene which varies between individuals must be detected." (Office Action, page 11). Applicant must respectfully disagree. Applicant provides an explicit definition and description of the phrase "genetic marker" in the Specification at page 24, paragraph 2, lines 5-10.

f) The Examiner argues that "Claims 2-6 are indefinite because it is unclear whether the course of action taken following generating a genomic profile may include abstaining from administering anesthesia, or whether the course of action will include administering anesthesia, however may include additional drug administration." (Office Action, page 12). To the contrary, these options are described with particularity in Specification Section I.D. "Applications and Interventions of Specific Markers." Examples of abstinence from specific anesthetics are provided at page 31, paragraph 3 lines 22-23: "If a subject is found to have a marker predictive of increased risk for MH (malignant hyperthermia), anesthetics known to trigger MH are avoided."; and at page 31, paragraph 1, lines 7-9 "If a subject's predisposition to impaired or accelerated P450 metabolism is known, adverse drug reactions can easily be avoided by *substituting* other medications or adjusting dosages." (emphasis added) - substitution represents abstinence from the contraindicated medication. An example of inclusion of additional drug administration is provided at page 32, paragraph 2, lines 16-18: "Prophylactic treatment (e.g. anti-coagulation medications, positioning, and compression devices) and closer monitoring can reduce the incidence and severity of thrombus." (emphasis added). For the above reasons, Applicant respectfully requests that these rejections be withdrawn.

D. THE CLAIMS ARE NOT ANTICIPATED

The Examiner has rejected the Claims as allegedly anticipated by several references. The Federal Circuit has stated the relevant analysis for anticipation as follows:

> "A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."[1]

[1] *Verdegaal Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987)

Applicant respectfully submits that none of the references cited by the Examiner teach each element of the Claims.

1. Vogelstein (US Pat 5,380,645, January, 1995) Does Not Anticipate the Claims

Claims 1, 13, and 17 are rejected under 35 U.S.C. SS102b as allegedly being anticipated by Vogelstein. The Examiner states that Vogelstein teaches "this perioperative subject, was subjected to an assay which identified two or more genetic markers, i.e. 7q, 18q and 20p in which a genetic profile was generated." (Office Action, pages 12-13). However, Applicant submits that Vogelstein does not teach **perioperative genomic profiling**. The present claims recite the element that the assay generate a genomic profile for use in selecting "a perioperative course of action." Vogelstein does not provide this element. Vogelstein teaches use of allelic loss in cancerous tissue for post-surgical oncologic (i.e. not perioperative) management. Vogelstein provides no teaching that the results of an assay lead one to take any specific type of perioperative course of action. Vogelstein's statement that "the measurement of allelic losses might help to identify patients with an otherwise relatively favorable prognosis who could benefit from additional therapy" provides no suggestion that the "therapy" be in the context of a "perioperative course of action." Even if one were to improperly interpret the "therapy" to be a surgery, Vogelstein would only be indicating that the results of the assay lead one to contemplate a surgery (i.e., this is not within a perioperative period, which as defined in on page 21 of the Specification, only begins after a surgery is contemplated) and provides no teaching or suggestion or any course of action during the perioperative period. It is further noted that Vogelstein does not state that the assay result provide any useful information about further therapy, but simply states they "might." Vogelstein also fails to teach or suggest assay results that find use in selecting a surgical procedure treatement course of action (Claims 13 and 17) or where the genetic markers are associated with a pharmacological response and the subject undergoes a surgical procedure treatment course of action using conditions based on the genomic profile (Claim 17). Therefore the claimed **perioperative genomic profiles** are distinguished from allelic loss in carcinomatous tissue by Vogelstein. For the above reasons, Applicant respectfully requests that the rejection be withdrawn.

2. Sachse *et al.* Does Not Anticipate the Claims

Claims 1, 8-10, 13-14 and 17 are rejected under 35 U.S.C. SS102(b) as allegedly being anticipated by Sachse *et al.* While the Examiner argues that Sachse *et al.*, teaches " . . . performing PCR reactions 1-4 of table 1 routinely to detect the most frequent PM alleles and a test for the CYP2D6 gene duplication." (Office Action, page 13), Sachse *et al.* does not provide a sample from a perioperative subject, and does not anticipate generating a genomic profile that is useful in selecting a perioperative course of action. The subjects of Sachse are not perioperative subjects, but instead are research subjects who were given drugs. Sachse does not teach that these subjects were to undergo surgery or that any information obtained from the assay could be used to alter a course of action during the perioperative period. Indeed, even for clinical drug treatment outside of the scope of surgery, Sachse does not teach that a clinician should use the information (i.e., even if the information is informative, other factors may lead one not to use it). Specifically, Sachse, teaches that CYP2D6 testing is still not used in clinical medicine and that the value of genotyping in clinical specialties where CYP2D6-metabolized drugs are frequently applied "will have to be evaluated" (page 293, second columns). In addition to lacking these essential elements of independent Claim 1, 13 and 17, Claim 8 addresses pharmacodynamic risk, Claim 14 addresses medical procedures, and Claim 17 addresses surgical procedures. Finally, Sachse *et al.* does not teach use of genomic profiles for general anesthesia, regional anesthesia or surgical treatments. Therefore the claimed **perioperative genomic profiles** are distinguished from PCR-based testing for a narrowly restricted panel of CYP2D6 alleles in Sachse *et al.* For the above reasons, Applicant respectfully requests that the rejection be withdrawn.

3. DeStefano et al. Does Not Anticipate the Claims

Claims 1, 8-17, 20 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by DeStefano *et al.* DeStefano *et al.* does not anticipate provision of a sample from a perioperative subject and does not teach a genomic profile that is useful in selecting a perioperative course of action. In addition, the alleles recited by DeStefano do not teach pharmacodynamic risk (Claim 8), pharmacokinetic risk (Claim 9), risk of a medical procedure (claim 14), or risk of surgical treatment (Claim 16, Claim 17). Therefore the instant

invention's claimed **perioperative genomic profiles** are distinguished from the narrowly restricted PCR-based testing for two alleles associated with thrombophilia as taught by DeStefano *et al.* For the above reasons, Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action of September 22, 2000 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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